VVM Innovation

Thermostability monitoring of vaccines for global supply
Why bother about temperature monitoring?

Objectives of the immunization supply chain

- **Availability of vaccines at the right place in the right time**
  - If undetected: Potential stockouts
  - If detected: 

- **Vaccines are potent and have not been impacted by temperature excursions**
  - If undetected: Potential damaged
  - If detected: May not achieve sero-conversion

- **Resources are used efficiently**

Temperature monitoring: detects excursions and can help avoid future excursions
Challenges in vaccine Cold Chain management
Challenges in vaccine Cold Chain management
Vaccine exposure to Heating & freezing
- Current reality

Too hot
“Easier to detect”

Health worker in Niger shows bottles with vaccine vial monitors. Source: WHO

What do we know from the EVM Data Analysis

Over 90% of storekeepers and health workers know how to read VVMs.

Too cold
“Harder to detect”

Continuous temperature monitoring

“What about excursions during weekends?”

Example Freeze indicators

Only 11% of facilities pack freeze indicators with deliveries of freeze-sensitive vaccines

Shake test. Source WHO
Vaccine Temperature Sensitivity

Heat sensitivity
- most sensitive
- least sensitive

Freeze sensitivity
- least sensitive
- most sensitive

Days at 37°C
- 2
- 7
- 14
- 30

Temperature Intelligence™ Solutions
Four WHO VVM Categories to Monitor Vaccines with Different Heat Sensitivities

**HEATmarker VVMs - Time to VVM Endpoint**

- **VVM2**
- **VVM7**
- **VVM14**
- **VVM30**

**Degrees C**

**Days**

**DAYS**

- 10000
- 1000
- 100
- 10
- 1

**DEGREES C**

0 5 10 15 20 25 30 35 40
Temptime Continues to Invest in Product Innovations

- VVM: new categories
- CTC & VVM\(^\text{TM}\): combined VVM and peak threshold indicator
- Hybrid 2D Bar Codes with embedded VVM active area: improve patient safety and address evolving international anti-counterfeiting/track & trace and serialization requirements
VVM7 - Improved

- VVM7 - improved
  - VVM7 naturally develops color at 5°C over the course of two years
  - Current specification is ≥ 2 years to end point at 5°C
  - Improved formulation for full label is ≥ 2 years 4 months to end point at 5°C and typical time of 2 years and 6 months
  - Improved formulation for dot construction is ≥ 2 years 8 months to end point at 5°C and typical time of 2 years and 10 months
  - Independent lab tests have been completed and dossier submitted to PQS
VVM Line Extensions to Address Programmatic Needs: VVM11

• Why VVM11
  • Some vaccines have stability > VVM7 but < VVM14
  • Some vaccines have moved to 3 year expiry date but with < 14 days at 37°C
  • Change to statistical modeling of vaccine stability can possibility lead to a lower VVM type
    • e.g., VVM14 now would revert to VVM7
  • VVM11 fills the gap between VVM7 and VVM14
    • Provides ≥ 2.5 years at 5°C
    • Project initiated based initially on potential IPV stability
• Status
  • Included in VVM spec revision to be published soon
## VVM New categories

<table>
<thead>
<tr>
<th>Type (Vaccines)</th>
<th>Maximum time to end point at +37°C</th>
<th>Maximum time to end point at +25°C</th>
<th>Maximum time to end point at +5°C</th>
<th>Time to end point at +5°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>VVM30: High Stability</td>
<td>30 days</td>
<td>193 days</td>
<td>NA*</td>
<td>≥4 years</td>
</tr>
<tr>
<td>VVM14: Medium Stability</td>
<td>14 days</td>
<td>90 days</td>
<td>NA*</td>
<td>≥3 years</td>
</tr>
<tr>
<td>VVM11: Intermediate stability</td>
<td>11 days</td>
<td>71 days</td>
<td>NA*</td>
<td>≥2.5 years</td>
</tr>
<tr>
<td>VVM7: Moderate Stability</td>
<td>7 days</td>
<td>45 days</td>
<td>NA*</td>
<td>≥2 years</td>
</tr>
<tr>
<td>VVM2: Least Stable</td>
<td>2 days</td>
<td>NA*</td>
<td>225 days</td>
<td>NA*</td>
</tr>
</tbody>
</table>

*VVM (Arrhenius) reaction rates determined at two temperature points.
Four Five WHO VVM Categories – VVM11 is Imminent

VVM11
The innovation of the Controlled Temperature Chain (CTC) – where do we go from here?

Anna-Lea Kahn - WHO-HQ/ EPI
14th TechNet Conference - Bangkok, Thailand
13 May 2015
The Next Challenge – Controlled Temperature Chain (CTC)

Objective: on-label use of vaccines in a CTC allowing specific vaccines to be kept and administered at ambient temperatures, up to 40°C for one, limited period of time

- All CTC pilot studies with
  - VVM on each vial
  - And Temptime’s LIMITmarker® threshold indicator in each vaccine carrier

Before Exposure to 40°C  
After Exposure to 40°C
New Product Innovations Address High Temperature Excursions

VVM+™

• Combined VVM response and high temperature threshold in a single indicator
HEATmarker VVM+
VVM Plus Peak Indicator in Same Device

- VVM+ reacts like a VVM up to 37°C
- At 40°C, VVM+ reaches the end point rapidly to show exposure to critical peak temperature
Comparison of VVM+ and VVM at Threshold Temperature
Four Five WHO VVM Categories and VVM+

VVM+ In Progress

Diagram showing the relationship between days and degrees Celsius for different VVM categories.
VVM Challenge –
Highly Stable Rotavirus Vaccine 540 days at 37°C

The thermo-stability of ROTASIIL®, ironically, has thrown up a new challenge in terms of vaccine vial monitors (VVM). The presently available VVM portfolio (Max VVM30: 30 days at 37 ºC) does not begin to cover the extreme thermo stability of ROTASIIL which is 18 months- (540 days) at 37 ºC. Efforts to develop a more appropriate VVM are on-going.

It has been already noted that there is remarkable reduction in mortality from diarrheal disease after vaccine introduction in
VVM Line Extensions to Address Programmatic Needs VVM250 – Technology Capability

Temptime has supplied TTIs for use by US Military with 3 year life at 26°C for more than 20 years and a more stable category for use on Rapid Skin Decontamination Lotion.

Additionally, the Joint Program Executive Office for Chemical and Biological Defense has developed a time temperature indicator (TTI) to include on RSDL packets when manufactured. TTIs incorporate MKT to accurately determine the service life limits of RSDL exposed to various temperatures. TTIs, therefore, assist with RSDL management by providing visible information reflecting product quality. An example TTI is shown in Figure 3.
VVM 250 – Upper limit of 250 days at 37°C

Draft WHO PQS specification would be:

<table>
<thead>
<tr>
<th>Maximum time to end point at +55°C</th>
<th>Maximum time to end point at +45°C</th>
<th>Time to end point at +25°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.0 days</td>
<td>73 days</td>
<td>≥ 900 days</td>
</tr>
</tbody>
</table>

New VVM category developed for thermostable vaccines!!
Four Five Six WHO VVM Categories and VVM+

VVM250

VVM11  VVM250
Strengthening the Immunization Supply Chain

2D Barcode with Embedded VVM
Transformational Innovation: 2D Barcode with Embedded VVM

Digitization of Chemical Indicators & Unit of Sale Level Data Connection

Enhance the value of 2D barcodes (for stock management, patient safety and anti-counterfeiting) by incorporating temperature integrity:

- Specific area has cumulative (VVM) and/or threshold ink printed as part of barcode
- Rapid reading with phone or scanner
- Connect with cloud based data set of other sensors

![2D Barcode with Embedded VVM Example](image)

### Tests Passed
- Monitor Category: VVM7
- Remaining Life: 80%
- Expiration Date: 2019-12-31
- Product Authenticity: ✓ OK
- GTIN: 10123451234512
- Batch Number: 16R00150
- Serial Number: 1234

![OneScan™ Temptime®](image)

### Tests Failed
- Monitor Category: VVM7
- Remaining Life: 0%
- Expiration Date: 2019-12-31
- Product Authenticity: ✓ OK
- GTIN: 10123451234512
- Batch Number: 16R00150
- Serial Number: 1234

![OneScan™ Temptime®](image)
GS1 2D Data Matrix with Threshold Sensor

• **Threshold Indicator** – rapid, irreversible color change when peak temperature threshold is exceeded

![Diagram showing threshold indicator below and exceed threshold temperature]

- Below threshold temperature
- Exceed threshold temperature

![GS1 2D Data Matrix images]

**Exceed Threshold Temperature**
GS1 2D Data Matrix with VVM

- **VVM** – gradual, irreversible color change from light to dark develops with cumulative time and temperature exposure.

Before heat exposure

After excessive heat

Time and temperature exposure
Demo of Data Matrix Processing - Status

- Developed and demonstrated algorithm on computer to decode binary change or measure color shades
- Developing app for phone or scanner
- GS1 organized a Working Group to create the Application Identifiers
Continuous End-to-End Temperature Monitoring with Dynamic 2D Barcode Indicator

Serialized barcodes on individual saleable units are a key enabling technology of global identification and tracking regulations.

The OneScan™ System

- Merges unit serialization and temperature monitoring in a single scan
- Improves stock management
- Enhances product integrity, patient safety, supply security and temperature compliance without inference

End-to-end unique identifier and unique temperature monitor
Dynamic Barcodes Allow Unit Level Data Connection from Manufacture to End Use

Product Flow

Package Level

Monitoring Device

Data Capture

Information Flow

Manufacturer

National Distributor

Local Distributor

Health Provider

Patient

Data Capture

Information Flow
The OneScan™ Value Proposition

Serving the needs of
• serialized supply chain tracking
• product authentication
• temperature assurance
• additional layer of anti-counterfeiting

Delivering new and sustainable value to the Life Sciences industry
Close collaboration with GS1 and AIM\(^1\) to Develop Standards for Temperature Sensors

**Update and next step Work Request:**

**Application Identifiers for temperature monitors**

WR 17-045

Tuesday 10 October 13:45-14:30 Brussels

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\(^1\)Association for Automatic Data Capture, Identification and Mobility
India EVM Assessment

- 2013 (latest assessment) shows good understanding of VVM but low scores on effective use of VVM for stock management.

- Scores have likely improved in recent years but 2D barcode with VVM would automate stock management processes and set the new standard for best practices.

Some of the aspects of the vaccine management which is very critical for safe immunization programme and performance scores are at very low level, like:

- All parameters of vaccines (type of vaccine, vial size, quantity received, vaccine manufacturer, batch number, expiry date of each vaccine batch, VVM status and location in the store) are not recorded and performance score ranges between 52-60% at PHC and District VS.

<table>
<thead>
<tr>
<th>Indicator wise Score</th>
<th>Aspects</th>
<th>4 GMSD</th>
<th>18 State / RVS</th>
<th>14 Divisions</th>
<th>28 Districts</th>
<th>52 HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of sites</td>
<td>E7.11a</td>
<td>0%</td>
<td>12%</td>
<td>8%</td>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>

**Do received vouchers have VVM and FI information**

<table>
<thead>
<tr>
<th>State / Region</th>
<th>Division</th>
<th>District</th>
<th>HF-1</th>
<th>HF-2</th>
<th>Stock level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raipur SJS</td>
<td>Surajpur District SJS</td>
<td>Normadavapur GH</td>
<td>Vaccine presentation and VVM status</td>
<td>Vaccine presentation, Manufacturer name and VVM status</td>
<td>Stock level</td>
</tr>
<tr>
<td>Vaccine status and VVM status available</td>
<td>Vaccine status and VVM status available</td>
<td>Vaccine presentation, Manufacturer name and VVM status</td>
<td>Vaccine presentation, Manufacturer name and VVM status</td>
<td>Vaccine presentation, Manufacturer name and VVM status</td>
<td>Stock level</td>
</tr>
</tbody>
</table>

**c. Stock keeping**

Diluent and VVM record keeping was not seen in majority of the vaccine stores.

Verify stock records for sufficiency of working and buffer stocks, and in and out transactions and ensure that immediate action is taken when buffer stock is breached.

All salient parameter of vaccine & diluents must be noted, particularly the:

- VVM stage (for vaccines).
- Manufacturer.
- Batch number and
- Expiry date.
Proof of Concept Pilot – Phase 1 under discussion

- Apply 2D barcode label with VVM on secondary cartons at manufacturer
- Scan cartons on shipment out and receipt at each transfer to district level using smartphone with OneScan™ app
- Automated data collection and digitized VVM readings
- Push data to the cloud

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1 Dr. Pradeep Haldar Ministry of Health and Family Welfare, India
15th TechNet Conference Portugal, 16-20th October, 2017
Standards, Serialization and Smartphones for Interoperability

- PoC design based on global standards for scalability and interoperability

Bar codes can help track and trace health products in the supply chain. But to do so efficiently, they should be based on global standards rather than a proprietary system, and the captured data should be integrated into national health information systems to achieve end-to-end data visibility.
Goal: Integrate Stock Management and VVM Data into National Programs with Global Interoperability

- After successful Phase 1 PoC on secondary carton, consider new phase on vial level with serialization

**eVIN (Electronic Vaccine Intelligence Network)**

In 2014, Pilot took place in Bareilly and Shajahanpur to digitalize vaccine and logistics stock.

As of now, **12 states, 371 districts** and around **11,000 Cold Chain points** along with **14,000 Temperature Loggers** installed in India. With a plan of Nation-wide scale-up.
THANK YOU!!!